Grading of Aortic Stenosis Severity: a head-to-head comparison between cardiac magnetic resonance imaging and echocardiography

Short title: Grading of AS by CMR

INTRODUCTION

Degenerative aortic valve stenosis (AS) has become one of the most common valvular heart disease in developed countries, and its prevalence is expected to increase due to aging of the population[1]. The most common cause of AS in adults is the calcification of trileaflet or congenital bicuspid valve apparatus.

In patients with AS, the precise determination of disease severity is of utmost importance for management and therapeutic decision-making[2-5]. Given that AS should be intended as a disease continuum and no single parameter alone should define severity, grading of AS is usually performed on the basis of a spectrum of non-invasive hemodynamic measurements, i.e. peak aortic jet velocity, mean pressure gradient, and aortic valve area (AVA). Particularly, aortic valve effective orifice area (EOA) and mean trans-valvular pressure gradient (MPG) evaluation are the cornerstone of AS assessment[5]. Current ACC/AHA[5] and ESC[4] guidelines recommend EOA< 1.0 cm^2 and MPG > 40 mmHg as the main criteria to define severe AS. Although the invasive quantification of AS severity by catheter-based hemodynamic techniques has been proposed as the gold standard for the grading of AS severity, today it is rarely performed because time-consuming, costly, and entailing substantial risk. In addition, it is well known that the use of the Gorlin's equation to estimate the AVA is associated with several sources of error, as being directly influenced by cardiac output, blood viscosity, and flow turbulence[6]. Further, the original purpose of Gorlin equation was to give an estimate of the anatomical AVA, but "what our eyes see is not necessarily what our heart feels", and EOA by continuity equation better represents the hemodynamic burden caused by the stenosis. Also, similar AVA geometries may lead to different EOA, accounting a non-trivial percentage of AS misclassifications. In daily clinical practice, transthoracic echocardiography (TTE) is the recommended imaging modality for the initial assessment of suspected aortic valve disease and for the evaluation of EOA and AVA (class I, Level of Evidence: B) [4,5,7].

Assessment of anatomical AVA by direct planimetry (AVApl) of the valve orifice is often necessary in questionable cases – importantly when assessment of EOA is unreliable due to poor transthoracic acoustic windows and/or suboptimal Doppler angle alignment with flow direction – and this is usually done by transesophageal echocardiography (TEE), or – more recently – by cardiac magnetic resonance (CMR). MR planimetry does not rely on blood flow velocity quantification, pressure gradients or geometrical assumptions, thus, CMR may provide valuable information, especially in patients with reduced cardiac output or other conditions affecting measured parameters[8]. CMR may also be used to assess the functional degree of AS severity, by using velocity-dependent analyses based on the continuity equation[9].

To date, only few studies have been performed to evaluate the accuracy of CMR for planimetric and continuity equation measurements of AVA in comparison with TTE and TEE. Therefore, in the present two-center study we performed a direct comparison between planimetric and continuity equation measurements of AVA as assessed by CMR, TTE and TEE, in a series of patients undergoing valve surgery, and examined inter-modalities diagnostic agreement and precision.

METHODS

Patient Population

This is a retrospective observational study with two-site – Chieti, Italy and Bristol, UK - enrollment of 31 consecutive patients (21 men, 10 women, mean age 69 ± 10 years) with symptomatic moderate-to-severe aortic valve stenosis first assessed by TTE, and scheduled for elective aortic valve replacement. Demographic, anatomic and hemodynamic data, as well as clinical presentation of patients studied are summarized in **Table 1**.

Exclusion criteria were: LVEF<50%, more than mild mitral valve disease or aortic regurgitation, dynamic LVOT obstruction, hemodynamic instability, rapid uncontrolled arrhythmia, New York Heart Association (NYHA) class IV, or any contraindication to CMR (pacemaker or severe claustrophobia), and poor 2D echocardiography image quality (**Fig. 1**).

Protocol

Patients were imaged with standardized TTE, TEE and CMR. In all patients, TTE, TEE and CMR were performed according to established and standardized protocols by qualified observers aware of patients' medical history, suspected underlying disease and major comorbidities, but who were blinded to the results of other examinations. All examinations in the same patient had to be performed within a time interval of 7 days. Imaging and acquisition protocols were in agreement with recommendations from the Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized Protocols [10]and with the American Society of Echocardiography Recommendations for Quality Echocardiography Laboratory Operations [11].

Transthoracic Doppler echocardiography (TTE)

TTE was performed using conventional ultrasound systems (Philips Sonos 5500 and Philips iE33 X5-1, Philips Healthcare, Best, the Netherlands) attached to 1-5 MHz transducers. Details of the methods here used are provided in the Online Supplemental Material.

Transesophageal echocardiography (TEE)

2D-TEE was performed using conventional ultrasound systems (Philips Sonos 5500 and Philips iE33 X7-2t) attached to 2-7 MHz transducers. AVA assessment by direct planimetry was obtained from the mid-esophageal aortic valve short-axis view. After the TEE probe was positioned in the esophagus at the level of the aortic valve, the transducer was rotated from 0° to 30-45° to obtain a short-axis cross-sectional view of the aortic valve. After selecting one frame, in which the maximum aortic valve opening was observed, with fine adjustments of the cutting plane to delineate the smallest aortic valve orifice, the inner borders of the valve leaflets were traced manually using a magnified view to measure the AVA. Calcifications were considered as part of the cusp tissue. Final measurements were averaged in at least 3 cardiac cycles.

CMR imaging

CMR imaging was performed on 1.5 Tesla MR scanners (Achieva; Philips Medical System, Best, the Netherlands; and Avanto, Siemens, Enlargen, Germany), each using a dedicated 8-element phased-array cardiac synergy coil for signal reception. After localization of the heart using 3-plane and oblique survey images, cine imaging was performed with a balanced steady-state free-precession (bSSFP) technique at 30 phases per cardiac cycle (by vectorcardiographic gating) in 8-14 parallel short-axis, and 2-chamber and 4-chamber (8 mm thickness, 0 mm gap). A 3-chamber view (for the LVOT) and an oblique coronal view cine-image (for the aortic outflow tract of the left ventricle) were also acquired. These images were used as localizers to plan 4 contiguous cross-sectional cine-images of the aortic valve between the outflow tract and the level of the valve tips (**Fig. 2**). Cine-images were acquired using a multislice cine-bSSFP pulse sequence with retrospective gating during multiple breath holds. Typical parameters of aortic valve cross-sectional cine-images included slice thickness of 6 mm, gap of -1 mm, TR/TE of 3.4/1.2 ms, flip angle 40°, number of excitations (NEX) = 1, yielding an in-plane spatial resolution of 1.4 mm x 1.4 mm. Subsequently, for the quantitative flow measurements, 2 through-plane breath-hold phase-contrast (sQFlow) images were planned using the high-resolution cine-images (slice thickness of 8 mm), and acquired in an axial plane in the LVOT at 10 mm below the aortic valve annulus (reference: 0 mm) and in the ascending aorta 10 mm above the annulus. MR (VTI and V) data acquired at this level are most strongly correlated with the ultrasound measures (VTI and V) in the LVOT and at the aortic valve[12,13]. Phase-contrast MR imaging parameters consisted of: TR/TE of 4.60-4.92/2.76-3.05 ms, flip angle 15°, 24 phases, pixel spacing 1.32–2.07 mm, slice thickness 10 mm and acquisition matrix of 256x208. Each phase-contrast velocity mapping acquisition produced 2 images: one magnitude image and one phase image. For each patient, peak aortic jet velocity measured by TTE was used to define CMR encoding velocity (CMR velocity encoding (VENC) = (1.25 to 1.5) x peak jet velocity) to optimally define resolution. Velocities were assessed with ‘through-plane’ velocity mapping above the aortic valve plane. Importantly, our phase mapping protocol included preliminary in-plane phase contrast (PC) analysis aimed at imaging trans-aortic flow direction and to assist in planning the appropriate location of subsequent perpendicular ‘through plane’ slabs[14]. Typically, the maximum VENC was 2 m/s for the LVOT and 6 m/s in the aorta. However, in case of aliasing, flow images were reacquired in steps of 50 cm/s. As the first VENC range is subjectively set depending on the expected velocity of the jet and in order to speed-up the scouting process, we ran flow mapping by selecting the VENC range based on transvalvular aortic peak velocity as measured by CW-Doppler on TTE. In each of the 2 participating centers, all measurements were independently performed in duplicate by two observers blinded to clinical, TTE and TEE results. Cardiac MR planimetry of the valvular orifice was performed by precisely delineating the inner edges of maximum systolic opening of the aortic cusps. EOA was computed from phase-contrast MR images using the simplified continuity equation[15,16]. For this purpose, regions of interest (ROIs) were drawn on each of the 24 phases of magnitude images to include the lumen of the LVOT (10 mm below the aortic valve annulus) and of the aorta (10 mm above the annulus), and peak velocities were computed (V). $LVOT_{CSA}$ was measured on the through-plane phase-contrast images acquired at 10 mm below the aortic valve annulus, manually delineating the inner borders of the LVOT lumen. AVA was then calculated with the following formula:

$$AVA = A_{LVOT} \cdot \left(\frac{V_{LVOT}}{V_{AO}} \right)$$

For each modality, the valve opening was judged to be moderately stenotic (1.0<AVA>1.5 cm^2), or severely stenotic (AVA<1.0 cm^2). In addition, for each modality, the valve morphology was defined by two reviewers, in consensus, as bicuspid or tricuspid.

Statistical analysis

Normal distribution was described as mean, standard deviation (SD) or 95% confidence interval (CI). Linear regression analysis was performed to describe correlations between the different techniques. Agreements between different methods were explored using Lin's concordance correlation coefficient (CCC) and with Bland-Altman analysis[17]. The CCC (ccc/rho_c/ρc) combines measures of precision and accuracy for agreement on continuous variables. The CCC is the product of the Pearson correlation coefficient (r) by a bias correction factor (Cb) coefficient. The Pearson correlation coefficient measures how far each observation deviates from the best-fit line, and is a measure of precision; bias correction factor measures how far the best-fit line deviates from the 45° line through the origin, and is a measure of accuracy. This coefficient ranges from zero (no agreement) to one (perfect agreement), without categorized levels for CCC values. For descriptive reasons, we here arbitrarily chose four categories for correlation: high ($\rho c \geq 0.8$), good ($0.7 \leq \rho c < 0.8$), fair ($0.6 \leq \rho c < 0.7$) and poor ($\rho c < 0.6$). We used Bland-Altman plots to graphically represent results obtained by two methods of measurement, which is useful to estimate and represent measurement errors graphically.

RESULTS

Patient Characteristics and Study Protocol

One patient was excluded from the study because of severe claustrophobia, two for LVEF<50% and one for poor 2D echocardiography image quality (**Fig. 1**). AVA, as assessed by CMR, ranged from 0.4 to 1.5 cm^2 (0.93 ± 0.42 cm^2). Twenty-four (77.5%) patients were classified by CMR as affected by severe AS, with AVA ≤1.0 cm^2. Of these, 8 (32.2%) patients had critical AS, with an AVA ≤0.75 cm^2. Out of 31 patients, 5 had bicuspid aortic valve disease, 24 "degenerative" AS and 2 rheumatic aortic valve disease. A total of 11 patients (all of whom with an AVA <1.2 cm^2) had grade 3 (moderate) or 4 (severe) calcifications on TTE. Mean values of AVA by the different methods used and concordance correlation coefficients are summarized in **Table 2** and **Table 3**, respectively.

Planimetric AVAs by CMR and TEE

Image quality of short-axis cine-CMR and TEE images through the aortic valve was uniformly estimated as good according to guideline criteria, and allowed successful planimetry of AVA in all 31 patients.
As shown in **Fig. 3a,b**, CMR planimetry (0.93 ± 0.42 cm^2) correlated highly with TEE planimetry (0.92 ± 0.32 cm^2), with a CCC of 0.85 (CI 95% 0.75-0.91). Excluding patients with moderately calcified (score 3) and extensive thickening and heavy calcification of all cusps (score 4) (**Fig. 3c,d**), the CCC increased to 0.93 (CI 95% 0.86-0.96).

Simplified continuity equation-derived EOAs by CMR and TTE

Measurements of the LVOT area by CMR were feasible in all 31 patients. As shown in **Fig. 3e,f**, EOA measured by continuity equation-CMR (0.86 ± 0.30 cm^2) was very similar to TTE-derived EOA (0.78 ± 0.25 cm^2) with a CCC of 0.82 (CI 95% 0.68-0.90). LVOT cross-sectional area obtained by TTE (3.3 ± 0.8 cm^2) resulted to be smaller than the area obtained by CMR (3.8 ± 0.7 cm^2), with a CCC = 0.71. Cardiac MR revealed that the LVOT shape was oval in the vast majority of patients (**Fig. 4**).

Comparison of Planimetric AVA and Continuity Equation-Derived EOAs

There was a good correlation between planimetric (both CMR and TEE-derived) AVAs and continuity equation-derived EOAs (by CMR and TTE). Planimetric measurements by CMR (0.93 ± 0.42 cm^2) and TEE (0.92 ± 0.32 cm^2) turned out to be significantly higher than corresponding values obtained with the continuity equation by CMR (0.86 ± 0.30 cm^2; $p<0.05$) and TTE (0.78 ±0.25 cm^2; $p<0.001$).

Comparison of Bicuspid and Tricuspid AVA

After the exclusion of 5 patients with bicuspid aortic valve, we observed no statistically significant differences in terms of CCC both between planimetric AVA at CMR and the same parameter at TEE (0.89 vs 0.85) and EOA at CMR and TTE (0.83 vs 0.82).
The analysis restricted to the few (n=5) patients with bicuspid aortic valve also revealed no statistically significant differences in terms of CCC both between planimetric AVA at CMR and TEE (0.79 vs 0.85) and EOA at CMR and TTE (0.78 vs 0.82).

Reproducibility

TTE and TEE measurements of the EOA and AVA were both repeated twice by the same observer 2 weeks after the first measurement. Both methods had similarly high intra-observer reproducibility (CCC=0.90 and 0.92, respectively). Cardiac MR measurements were repeated twice immediately after the examination by one single observer. To investigate the inter-observer variability of CMR measurements, a second observer performed the measurements offline, blinded to the results of the first observer. CMR planimetry intra- and inter-observer reproducibility was excellent (CCC=0.94 and 0.91, respectively). Intra- and inter-observer reproducibility of EOA was also excellent (CCC=0.92 and 0.90, respectively).

DISCUSSION

We here demonstrate the overall high concordance of measurements of aortic valve areas with a totally non-invasive technique, CMR, using both planimetry and continuity equation, as compared with evaluations derived by 2D echocardiography. Also, we here demonstrate the increased agreement of CMR-derived planimetry after excluding patients with thickened and moderately/heavy calcified valves, which is one limitation to bear in mind when performing CMR analyses. In such cases, the continuity equation-derived evaluation appears to be the strategy of choice for CMR in grading the severity of isolated AS.

Echocardiographic assessment of AS severity by use of the simplified continuity equation or planimetry

The 2D transesophageal planimetric method is known to be more accurate than the similar 2D transthoracic method. Although attractive, direct planimetry of the AVA by TEE is technically rather demanding. It indeed requires a precise positioning of the transducer to obtain the correct cross-sectional view at the level of the edges of the aortic cusps at their maximum opening, which can be quite challenging due to the aortic root anterior and superior movement during the cardiac cycle. Also, an accurate delineation of the leaflet edges can be difficult in cases of severely calcified leaflets. Currently, the preferred non-invasive method for grading AS severity is Doppler-echocardiography with the use of the continuity equation[5]. Based on this principle, to calculate the EOA one needs to perform 3 measurements: the VTI of the LV outflow tract using PW Doppler, the VTI through the aortic valve using CW Doppler, and the cross-sectional area of the LVOT, which is calculated from the measured LVOT diameter by assuming a circular shape. Calculation of the EOA by using the simplified continuity equation has some disadvantages, as it may not be feasible in a significant proportion of patients due to poor acoustic window and/or subvalvular flow acceleration. Moreover, given that the calculation of AVA requires the inclusion of 3 measurements (the LVOT diameter, the LVOT peak velocity and the aortic peak velocity) in the simplified continuity equation, this method may involve relatively large measurement errors. The precise estimation of LVOT diameter is the most critical parameter for an accurate estimation of the EOA, and is difficult in patients with poor acoustic windows or severe calcifications of the aortic valve and of the outflow tract. TTE also assumes a circular shape of the LVOT, and uses the smaller antero-posterior diameter to compute the LVOT area. In contrast, CMR imaging reveals that the LVOT shape is elliptical in the vast majority of patients (**Fig. 4**). In addition, measurement of the peak flow velocity in the LVOT may be distorted in patients with high or low left cardiac output or associated valvular insufficiency, because it is susceptible to changes in flow dynamics. Because of these limitations, the direct AVA planimetry has been proposed as an alternative method. Today, this is best achieved with the use of multiplane TEE[18,19], which is however technically demanding for the aforementioned reasons. This highlights the important need for additional non-invasive and accurate methods for the fine assessment of stenosis severity in the presence of possible discordances between TTE-EOA measurements, transvalvular gradients, dimensionless velocity ratio, and eventually clinical findings.

Assessment of AS severity by CMR

Because of the aforementioned limitations of echocardiography, several investigators have recently proposed to grade the severity of AS by using CMR. Indeed, with the introduction of SSFP, CMR allows high-quality cine-short-axis images of the aortic valve, and therefore to obtain accurate direct planimetry of its maximum opening area.

Several recent studies have compared the measurements of AVA obtained by this planimetric approach with those obtained by TEE. All such studies have demonstrated a good agreement between CMR and both echocardiographically-derived planimetric AVA or EOA [12,20-23]. Potential limitations of CMR planimetry are difficulties in the precise visualization of the aortic cusps due to partial volume effects, the presence of calcifications, or flow-related artefacts. SSFP sequences are generally preferred because of their superior signal-to-noise ratio, clear-cut blood-tissue contrast, and high spatial and temporal resolutions, making the accurate identification of the fast-moving valve cusps easier[24]. Indeed, von Knobelsdorff-Brenkenhoff et al. have demonstrated that also CMR planimetry of aortic bioprosthetic orifice area correlates highly with data obtained by TTE (r=0.82) and TEE planimetry (r=0.92) despite artefacts caused by the presence of surgical foreign bodies, such as sternal wires and the struts of stented prostheses[25].

As shown in **Table 4,** the agreement between CMR and TEE to assess native aortic valves in our study (CCC=0.85) is as high as those reported by Debl et al. (r=0.86)[23], John et al. (r=0.96)[21], and Pouleur et al. (r=0.98)[26]. However, an original aspect of our results is the increase of CCC (from 0.85 to 0.93) after the exclusion of patients with extensive thickening and moderate-to-severe calcification of the aortic valve apparatus (Rosenhek grade 3 to 4). This result highlights a potential limitation of the CMR planimetric techniques, as diffuse valvular calcifications may hamper the correct delineation of the leaflets and the estimation of the valve area.

Besides the direct planimetry of the aortic valve opening, CMR also allows the EOA calculation by use of the continuity equation. As with Doppler echocardiography, this requires the obtainment of 2 different sets of data, i.e., supra- and sub-valvular flow velocity data, which can be obtained by the use of velocity-encoded phase-contrast images, and anatomical information on the dimensions of the LVOT, which requires multislice cine-imaging.

Multidetector computed tomography is a powerful imaging modality to measure dimensions, surfaces and volumes of cardiac chambers. However, this method does not allow measurement of flow velocities, thereby not permitting the determination of continuity equation-derived AVA. Conversely, CMR is a non-invasive, radiation-free imaging modality that allows the quantification of flow velocities. Moreover, CMR has superior temporal resolution as compared with computed tomography. EOA measured by continuity equation-CMR and TTE are well correlated, with a CCC of 0.82. Noticeably, the LVOT cross-sectional area obtained by TTE (3.3 ± 0.8 cm^2) resulted smaller than the area obtained by CMR (3.9 ± 0.7 cm^2), with a CCC of 0.71. Pouleur et al. reported that CMR yielded larger LVOT diameter values [25]. Unlike the studies by Pouleur et al.[26] and Paelinck et al.[27], we measured the LVOT area on the through-plane phase-contrast images acquired at 10 mm below the aortic valve annulus, manually delineating the inner borders of the LVOT lumen and not the LVOT diameter. Thanks to this method, we show that the LVOT cross-section is typically elliptical and not circular; as a consequence, TTE underestimates the LVOT area calculated assuming a circular geometry. This is in agreement with conclusions derived from 3-D echocardiography[28] and from another comparison of TTE and CMR[29].

Planimetric AVA vs continuity equation-derived EOA

We found a good correlation between planimetric AVA (both by CMR and TEE) and continuity equation-derived EOAs (both by CMR and TTE). Planimetric measurements by CMR (0.93 ± 0.42 cm^2) and TEE (0.92 ± 0.32 cm^2) turned out to be significantly higher than those obtained by continuity equation at CMR (0.86 ± 0.30 cm^2; $p<0.05$) and TTE (0.78 ± 0.25 cm^2; $p<0.001$). Our results are consistent with those of Pouleur et al.[26], who reported that the EOA values calculated by the continuity equation (TTE and CMR) were systematically slightly lower than the values derived by planimetry (TEE and CMR). This observation is not surprising, since direct planimetry reflects the anatomical orifice area, while the calculated EOA reflects the functional orifice area. The latter indeed reflects the cross-sectional area of the *vena contracta* of the transvalvular flow jet. The EOA is generally smaller than the AVA because there is a contraction of the flow downstream of the valve orifice (1-3).

Clinical Implications

Despite different techniques are available for the grading of AS severity, a “gold standard” is still lacking, since all available techniques have their limitations. In TTE, inaccurate measurements can be related to a poor acoustic window, extensive valvular calcifications and the assumption of a circular shape of LVOT. Likewise, the peak transvalvular velocity may be missed if the ultrasound beam is not directed parallel to the velocity jet. TEE is a semi-invasive method. Furthermore, in patients with heavily calcified aortic valves the exact delineation of the leaflets and the exact planimetry of the AVA are hampered. CMR overcomes most of the above-mentioned methodological limitations, especially using SSFP white-blood sequences, which allow an accurate delineation of valvular structures and of the orifice area, and in addition potentially detects myocardial fibrosis and infarction (4). Nevertheless, it still has limitations in its contraindication, such as the presence of metal implants (now largely overcome), arrhythmias and claustrophobia. In practice, TTE is likely to remain the non-invasive, ubiquitously available and cost-effectively preferred technique for the initial evaluation of patients with suspected valvular heart disease in daily clinical practice. However, as shown by the present study, for a second-tier evaluation CMR may provide accurate data on AVA and EOA in patients with poor acoustic windows or in the presence of discordance between data obtained by TTE and clinical findings (5,6). In addition, due to the opportunity of revealing areas of fibrosis and/or necrotic myocardium by late gadolinium enhancement, as well as to assess myocardial perfusion, not provided by standard TTE, CMR may be the preferred test for assessing patients with multiple cardiac abnormalities. In this setting, the assessment of valve stenosis severity becomes an important component of a comprehensive cardiac examination.

Several recent studies have reported that multidetector computed tomography (CT) planimetric measurements of AVA are highly reproducible and correlate strongly with CMR and TEE planimetry and was very similar to the continuity equation TTE-derived AVA thanks to high spatial resolution which allow precise delineation of the free edges of the valve. It also allows accurate in vivo quantification of aortic valve calcifications[30]. Multidetector CT has two great limitations, represented by the radiation exposure and the impossibility to obtain transvalvular flow and velocities, hence preventing us from obtaining effective orifice area measurement. Conversely, CMR is a non-invasive, radiation-free imaging modality that allows quantification of flow velocities. Moreover, CMR has superior temporal resolution as compared with computed tomography[31,32].

Study Limitations

We acknowledge limitations in the present study. Firstly, the relatively small number of patients enrolled in our study prevented us from performing subgroups analyses in patients with different flow-gradient patterns. Further studies are warranted to investigate this issue. Secondly, we included 5 patients with bicuspid aortic valve, a condition known to be associated with complex flow patterns which may affect the accuracy of flow measurement by PC imaging. However, we used the simplified continuity equation method to derive AVA and in-plane PC to assist in planning the appropriate location of subsequent perpendicular 'through plane' slabs in order to calculate the highest jet velocity. Thirdly, we acknowledge 3D-TTE may provide with a better measurement of the LVOT likely improving accuracy and precision of EOA determination[33].

Conclusions

The compared planimetric AVA and continuity equation-derived estimates of EOA by CMR and echocardiography in this study demonstrate the potential of CMR as a promising and non-invasive alternative diagnostic tool for the evaluation of AS in patients unsuitable to TTE examination, in the presence of discordances between TTE-derived parameters and clinical findings, or in patients in whom CMR is advised for additional clinical reasons.

DECLARATIONS

Abbreviations

AVA = anatomical aortic valve area
AS = aortic valve stenosis
EOA = effective orifice area
CMR = cardiac magnetic resonance
TTE = transthoracic echocardiography
TEE = transesophageal echocardiography
CT = computed tomography
bSSFP = balanced steady-state free precession
PC = phase-contrast
VENC = encoding velocity
CCC = concordance correlation coefficient
LVEF = left ventricular ejection fraction
LVOT = left ventricular outflow tract
LVOT-CSA = outflow tract cross-sectional area
VTI = velocity time integral
V = peak jet velocity
VAO = Peak aortic jet velocity
VLVOT = peak left ventricular outflow tract jet velocity
SV = stroke volume

Compliance with Ethical Standards

No funding sources to be acknowledged from the Italian team. The part of this work performed in the UK was partially supported by the NIHR Bristol Cardiovascular Biomedical Research Unit (to Dr Chiara Bucciarelli-Ducci).

Conflict of Interest

No conflicts of interest as to the content of this manuscript reported by any of the authors.

Ethical approval

All procedures performed in studies here presented and involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
Informed consent for the performance of the diagnostic examinations here reported was obtained from all individual participants included in the study.

Ethical Approval and Consent to participate

Not applicable: retrospective analysis of data acquired for clinical purpose: as such, approval from the local Ethics Committee was not necessary and was not sought.

Consent for publication

All Authors have agreed on the publication of the material, and left to the Corresponding Author the choice of where to submit the manuscript.

Availability of supporting data

Original material available upon request – See also the Online Supplemental Material.

Competing interests

No competing interest from any of the coauthors

FIGURE LEGEND

Fig. 1: Study population flowchart.

Pts = patients; LVEF = left ventricular ejection fraction; TTE = transthoracic echocardiography; CMR = cardiac magnetic resonance; TEE = transesophageal echocardiography; AVA = aortic valve area; EOA= effective orifice area.

Fig. 2: Slice positioning for planimetry of the aortic valve at cardiac magnetic resonance (CMR).

Oblique coronal (a) and 3-chamber long axis view (b) of the aortic outflow tract with slice position for planimetry indicated by white lines parallel to the aortic annulus. Cross-sectional bSSFP image (c) show a stenotic tricuspid valve.

Fig. 3: Statistical analysis of concordance between measurements performed.

Linear regression **(a)** and Bland-Altman analysis **(b)** illustrating the agreement between AVA assessed by planimetric measurements (CMR and TEE). Linear regression **(c)** and Bland-Altman analysis **(d)** illustrating the agreement between AVA assessed by planimetric measurements after exclusion of patients with extensive thickening and heavy calcification of all cusps. Linear regression **(e)** and Bland-Altman analysis **(f)** illustrating the agreement between EOA assessed by simplified continuity equation (CMR and TTE). AVA = aortic valve area; CMR = cardiac magnetic resonance; EOA= effective orifice area; TEE = transesophageal echocardiography.

Fig. 4: Measurements of LVOT cross-sectional area.

Slice positioning for LVOT cross-section area measurements by CMR sequences acquired in a short-axis plane 10 mm below the aortic valve annulus. CMR revealed that LVOT have an oval and not circular shape. LVOT = left ventricular outflow tract.

Table 1: Demographic, anatomic and hemodynamic data of the study population	
Gender	Male 21, female 10
Age (years, mean ± SD)	69 ± 10
LVEF (%, mean ± SD)	63.5 ± 18.6
LVEF ≤ 50% (n)	5
TTE-AVA (cm^2, mean ± SD)	0.93 ± 0.43
Valve morphology (n)	Tricuspid 26, bicuspid 5
Valve calcification* (n)	No 3, Mild 7, Moderate 10, Severe 11
Leaflets thickness (mm, median (range))	4.3 (0.5 - 8.5)
Aortic insufficiency (n)	No 16, Mild 10, Moderate 3, Severe 2
Mitral insufficiency (n)	No 15, Mild 11, Moderate 3, Severe 2

Abbreviations: SD = standard deviation; LVEF = left ventricular ejection fraction; TTE-AVA = transthoracic echocardiography-aortic valve area.

* Grading according Rosenhek et al, (Online Supplement Ref. 4)

Table 2: Mean values of AVA by the different methods investigated in this study

Method	Mean ± SD	n
pl-cMR	0.93 ± 0.42 cm^2	31
TEE	0.92 ± 0.32 cm^2	31
ce-cMR	0.86 ± 0.30 cm^2	31
TTE	0.78 ± 0.25 cm^2	31

Abbreviations: AVA = Aortic valve area; SD = standard deviation; pl-cMR = planimetry by cardiac magnetic resonance; TEE = transesophageal echocardiography; ce-cMR = continuity equation by cardiac magnetic resonance; TTE = transthoracic echocardiography.

Table 3: Concordance correlation coefficients between the different methods investigated in this study

Methods compared	CCC
pl-cMR and TEE	0.85 (95% CI 0.75-0.91)
* Excluding patients with heavily calcified valve	0.93 (95% CI 0.86-0.96)
ce-cMR and TEE	0.79 (95% CI 0.63-0.89)
ce-cMR and TTE	0.82 (95% CI 0.68-0.90)
pl-cMR and TTE	0.70 (95% CI 0.47-0.83)
pl-cMR and ce-cMR	0.76 (95% CI 0.61-0.85)

Abbreviations: CCC = concordance correlation coefficient; CI = confidence interval; pl-cMR = planimetry by cardiac magnetic resonance; TEE = transesophageal echocardiography; ce-cMR = continuity equation by cardiac magnetic resonance; TTE = transthoracic echocardiography.

Table 4: Comparison of findings of the present studies with previous studies comparing performances of cMR with other techniques for the assessment of aortic stenosis

First author, year Reference	Our study, 2015	Garcia J et al., 2011 24	Pouleur AC et al., 2007 20	Debl K et al., 2005 17	Kupfahl C et al., 2004 16	Caruthers SD et al., 2003 9	John AS et al., 2003 15	Friedrich MG et al., 2002 14
Sample size (n)	31	31	31	33	44	24	50	25
Age (mean ± SD)	69 ± 10	67±12	67±13			58 (range 34 to 84)	70±8.8	64±8
AVA (cm^2, mean ± SD)	0.93 ± 0.42	1.59±0.73	1.8±1.3	0.85±0.3	0.80±0.25		0.91± 0.25	0.82±0.23
AVA (cm^2, range)		0.72 to 1.73	0.43 to 6.05		0.45 to 1.40	0.5 to 1.8	0.5 to 1.6	0.40-1.30
Bicuspid valve (n)	5	9	10				1	5
AVA techniques comparisons								
- pl-cMR vs pl-TEE	CCC=0.85 (CCC=0.93)*		r=0.98	r=0.86	MD±SD=0.02±0.21 cm^2		r=0.96	
- ce-cMR vs ce-TTE	CCC=0.82	r=0.92	r=0.98			r=0.83		
- pl-cMR vs ce-TTE	CCC=0.70				MD±SD=0.05±0.20 cm^2			r=0.52
- pl-cMR vs cardiac catheterization				r=0.80			r=0.64	r=0.78
- pl-TEE vs cardiac catheterization					MD±SD=-0.05±0.26 cm^2		r= 0.58	
planimetric vs ce-derived methods	AVA overestimation by pl-methods (cMR and TEE)		AVA overestimation by pl-methods (cMR and TEE)	AVA overestimation by pl-methods (cMR and TEE)	AVA overestimation by pl-methods (cMR and TEE)			AVA overestimation by pl-methods (cMR and TEE)
cMR-LVOT vs TTE-LVOT	TTE underestimated the LVOT area; CCC=0.71	TTE underestimated the LVOT area; bias=-0.94 cm^2	TTE underestimated the LVOT area; r=0.92					

Abbreviations: cMR = cardiac magnetic resonance; SD = standard deviation; AVA = aortic valve area; pl-cMR = planimetry by cardiac magnetic resonance; pl-TEE = planimetry by transesophageal echocardiography; ce-cMR = continuity equation by cardiac magnetic resonance; ce-TTE = continuity equation by transthoracic echocardiography; CCC = concordance correlation coefficient; MD = mean difference; LVOT = left ventricular outflow tract.

*Excluding patients with extensive thickening and heavy calcification of all cusps, the CCC increased to 0.93.

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